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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/772,076	02/03/2004	Howard F. Bunn	18989-032	5061

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/772,076	BUNN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,11,13,16,18-21,23-25,31-37,45,50,52 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,11,13,16,18-21,23-25,31-37,45,50,52 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner in this application has changed. Please direct correspondences to Examiner Michael C. Wilson, Art Unit 1632.

Applicant's arguments filed 8-27-07 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 2-8, 10, 14, 15, 17, 22, 26-30, 38-44, 46-49, 51 and 54-59 have been canceled. Claims 1, 9, 11, 13, 16, 18-21, 23-25, 31-37, 45, 50, 52 and 53 remain pending and are under consideration.

Specification

The description of the drawings as amended on 8-27-07 still has errors because the descriptions of Fig. 1, 2, 3 and 5 do not correspond to the drawings filed 2-3-04. Fig. 1 is a picture of a gel. Fig. 2A is a vector, Fig. 2B-E are pictures, Fig. 3 and 5 are graphs. The Brief Descriptions of Fig. 1, 2, 3 and 5 as amended do not correspond to the figures.

Claim Objections

Claims 1, 13, 16, 21, 31 and 45 are objected to because they encompass non-elected subject matter (i.e.-*in vitro* and *ex vivo* methods). Contacting cells or tissue with the polypeptide of SEQ ID NO: 2, 3, 4 or 5 as in claims 1, 31 and 45 does not clearly set forth that the polypeptide is administered to a subject. The phrase "an in vivo method" in claims 1 and 31 is in the preamble and does not have to occur, and the body of the

claims does not clearly set forth the polypeptide is administered to a subject. Administering a compound that "increases expression or activity of Ncb5or" in claims 9, 16 and 21 does not clearly set forth the polypeptide is administered to the subject. Contacting cells with a composition that "increases expression or activity of Ncb5or" in claim 13 does not clearly set for the Ncb5or is administered to a subject. Correction is required.

Claims 13, 16 and 21 are objected to because administering Ncb5or does not increase expression of Ncb5or as encompassed by the claims.

Claims 9, 13, 16 and 21 are objected to because administering a composition that "increases activity of Ncb5or" does not clearly set forth that the method requires the active step of administering Ncb5or.

Claims 11, 18 and 23 are objected to because Ncb5or is not an "inducer of Ncb5or expression." The claims should clearly set forth that Ncb5or is administered to the subject.

Claim Rejections - 35 USC § 112, 1st Paragraph

Written Description

The rejection of claims 1, 31-37 and 45 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in favor of the following written description rejection. The rejection was withdrawn in part because claims 1, 31 and 45 have been limited to SEQ ID NO: 2, 3, 4 or 5, which have been described by applicants.

Claims 1, 9, 11-13, 16, 18-21, 23-25, 31-37, 45, 50, 52 and 53 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide any indication that full length Ncb5or (SEQ ID NO: 2), a heme oxide reductase, increases insulin, decreases glucose, inhibits beta cell loss, inhibits cell death or treats diabetes when administered to a subject in vivo. The specification shows that deletion of the Ncb5or gene leads to insulin deficiency in knockout mice (p. 7, lines 29-30) and that Ncb5or is widely expressed in many organs (p. 8, lines 6-7). Overall, the specification has merely provided a starting point for further research by indicating Ncb5or may play a role in the complex realm of diabetes. The specification does not teach the function of Ncb5or, where Ncb5or plays a role within the complex world of diabetes or that Ncb5or mutations are actually linked to humans with diabetes. The specification has not taught that administering Ncb5or in vivo will increase insulin, decrease glucose, inhibit beta cell loss, inhibits cell death or treat diabetes. In particular, the specification has provided no reasoning that Ncb5or would have the functions claimed in a subject with wild-type Ncb5or. Without such guidance, applicants have not provided adequate description that administering Ncb5or (SEQ ID NO: 2) in vivo will increase insulin, decrease glucose, inhibit beta cell loss, inhibit cell death or treat diabetes, particularly in a subject with wild-type Ncb5or.

Furthermore, the specification does not provide any indication that SEQ ID NO: 3 (the cyt b5 domain of SEQ ID NO: 2), SEQ ID NO: 4 (the hinge region of SEQ ID NO: 2), or SEQ ID NO: 5 (the cyt brR domain of SEQ ID NO: 2) (paragraph bridging pg 3-4) share the same function as full length SEQ ID NO: 2 and are capable of increasing insulin, decreasing glucose or treating diabetes, inhibiting beta cell loss, inhibiting cell death as claimed.

An adequate written description of a method requires more than a mere statement that it is part of the invention and reference to the protein and to its potential role in diabetes; what is required is adequate description of that administering SEQ ID NO: 2-5 will increase insulin, decrease glucose, inhibit beta cell loss, inhibit cell death or treating diabetes. It is not sufficient to merely state knocking out Ncb5or causes diabetic-like conditions, then conclude that administering SEQ ID NO: 2-5 in vivo increases insulin, decreases glucose, inhibits beta cell loss, inhibits cell death and treats diabetes, because disclosure of no more than that, as in the instant case, is simply a wish to know whether the proteins have those biological property. In particular, applicants fail to link the method to subjects having normal Ncb5or activity. Naming a method generically known to exist, in the absence of adequate knowledge as to whether the method works, particularly in subjects having normal Ncb5or activity, is not a description of that method. Thus, claiming all methods of administering SEQ ID NO: 2-5 that increase insulin, decrease glucose or treat diabetes without adequately describing the function of the proteins or that the method will work is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has

arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Enablement

Claims 1, 9, 11-13, 16, 18-21, 23-25, 31-37, 45, 50, 52 and 53 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of increasing insulin production, alleviating a symptom of diabetes, decreasing serum glucose levels, inhibiting a loss of beta cells, and inhibiting cell death, comprising administering or contacting pancreatic cells with Ncb5or.

The specification teaches that deletion of the oxidoreductase Ncb5or gene leads to insulin deficiency in mice (p. 7, lines 29-30). The specification teaches that Ncb5or is widely expressed in many organs (p. 8, lines 6-7); however, despite its ubiquitous expression, targeted ablation of Ncb5or in mice results in the very specific phenotype of severe diabetes with pronounced impairment of insulin production in beta cells. Specifically, Ncb5or-/- mice have a phenotype similar to maturity onset diabetes in the young (MODY). Animals up to one month of age have normal blood sugar levels, however by 8 weeks of age the mice develop severe hyperglycemia with marked reduction of plasma insulin. The mice are glucose intolerant and are insulin responsive. The animals have a decrease in white adipose tissue and a reduction of

body mass of about 15% compared to the littermate controls. In contrast they have normal amounts of brown adipose. In addition, the animals have an increase in serum trigycerides and serum cholesterol (p. 8, 12-20).

Neither the specification nor the art teach that treating a diabetes mouse model or a diabetic individual with Ncb5or will increase insulin production, alleviate a symptom of diabetes, increase serum insulin levels, decrease serum glucose levels, inhibit a loss of beta cells in pancreatic islet tissue, and inhibiting cell death as claimed. In particular, the specification and the art do not teach administering Ncb5or will treat diabetes in the absence of an Ncb5or knockout, i.e. administering Ncb5or to diabetic subjects having mutations in other genes may not treat their diabetes.

The knockout Ncb5or mouse disclosed in the specification provides a clue that Ncb5or may play a role in diabetes. It does not indicate humans with an Ncb5or have diabetes or that administering ncb5or to any patient with diabetes will increase insulin, decrease glucose, inhibit beta cell loss or inhibit cell death as claimed. Applicant has not established that any or all animals with diabetes or symptoms thereof are lacking Ncb5or activity or that they would benefit from increased Ncb5or activity.

The specification and post-filing art discloses methods for determining if a mutation and variants of the Ncb5or gene are associated with diabetes in human diabetes population. The specification discloses that Ncb5or was not contributing to the NOD mouse diabetes susceptibility (p. 24 lines 22-23). Andersen which includes the instant inventor as coauthors in this publication indicates that variation in the coding region of Ncb5or is not a major contributor in the pathogenesis of diabetes (Diabetes

53(11):2992-2997, 2004, see abstract). Therefore, it is unclear that Ncb5or plays any role in diabetes.

Further evidence of uncertainty about the relationship between Ncb50r knockout mice and how its phenotype relates to the disease state of diabetes arise in consideration of potential deleterious factors that may be contributed to from the background of the transgenic Ncb5or knockout mouse. The specification discloses that the phenotype of Ncb5or -/- animals was studied in three genetic backgrounds: C57BL/6+129, Balb/c+129, and pure 129, prepared by backcrossing chimeric animals with demonstrated germline transmission of the targeted gene into 129 wild type mice. All of the results presented below pertain to male animals with BALB/cAnN; 129 genetic background. The identical diabetic phenotype has also been seen in male and female C57BL/6;129 Ncb5or -/- and 129 Ncb5or -/- animals. None of the BALB/cAnN;129 Ncb5or -/- mice had any abnormalities on gross or microscopic examination or extensive clinical laboratory evaluation except those noted below (p. 20, lines 16-23).

The art teaches that both the C57BL/6 and 129, the strains most commonly used in making knockout animals have a predisposition of hyperinsulinemia, insulin resistance, and other symptoms associated with diabetes. Leiter et al (Diabetologia 45:296-308, 2002) teaches C57BL/6 mice are diabetes susceptible and commonly know to enhance diabetic phenotypes in knockout mice models of diabetes (p. 298, col 2, par 2). Leiter also teaches that the 129 strain genome harbours latent, undefined diabetes susceptibility quantitative trait loci capable of enhancing the deleterious

effects of reduced insulin receptor signaling (p. 299, col 1). Leiter et al also teaches a beta-2-microglobulin knockout mouse wherein, B6;129 genetic background admixture was the basis for the observed "autoimmune diabetes" rather than the presence of absence of beta-2-microglobulin gene (p. 300, col 1). Therefore, the art clearly indicates that the B6, the 129, and the b6/129 cross backgrounds all have the ability to contribute in a diabetes phenotype. Given that this is the background of all the mice expressing a diabetic phenotype, it is unclear to what extent the Ncb50r disruption and or the genetic background contributes to the reported phenotype in the Ncb50r knockout mouse which is the basis of the instant invention.

Further evidence to the uncertainty of the enablement of the instant invention is seen in WO 03/087399 (of record in the IDS). This WO document disclosed a treatment of diabetes comprising administering an inhibitor or antagonist of NADPH oxidase or NADPH oxidase complex (p. 7, par 1). They further disclose NADPH oxidase or NADPH oxidase complex can be (b5+b5r) oxidoreductase of SEQ ID NOs: 16 which is homologous to the SEQ ID NOS: 3-5 of the instant application (p. 7, par 8) or an Ncb5or polypeptide. Therefore, since the instant method is a means of enhancing expression of Ncbor5 to alleviate symptoms of diabetes, this is in conflict with the WO 03/087399 which provides an inhibitor to alleviate symptoms of diabetes. Therefore, from the disclosure in the art and the contradictory disclosure in the specification, an artisan would not know whether Ncb5bor administration would have the functions claimed.

The breadth of claims 16 and 21 encompass to the treatment of any subject. However, the specification and other claims are limited to increasing insulin production in pancreatic cells or alleviating symptoms of diabetes. Therefore an artisan would not know how to increase insulin or decrease glucose to any subject by administering Ncb5or to any subject or by contacting any cells than beta cell of the pancreas.

Overall, the specification does not enable those of skill to use the methods claimed to increase insulin, decrease glucose, alleviate symptoms of diabetes, inhibit loss of beta cells or inhibit cell death in vivo because it does not provide adequate guidance regarding the function of Ncb5or, does not teach the role of Ncb4or within the complex realm of diabetes, or that Ncb5or mutations are linked to humans with diabetes. Without such guidance, applicants have not provided the blaze marks for those of skill to determine the function of Ncb5or or the role of Ncb5or within the complex realm of diabetes. Accordingly, it would have required those of skill undue experimentation to determine the function of Ncb5or or the role of Ncb5or in the realm of diabetes. As such, the specification does not enable those of skill to use the methods claimed to increase insulin, decrease glucose, inhibit cell death, inhibit beta cell loss or alleviate symptoms of diabetes.

Applicants say the examiner states "an observed phenotype that is the result of a gene deletion does not mean that treatment of a subject with a compound that replaces the deleted gene results in the alleviation of the observed phenotype." Applicants' summary of the examiner's position is erroneous. The examiner rejected the claims because the specification does not provide adequate guidance that

administering Ncb5or in vivo to any subject as broadly encompassed by the claims will have the functions claimed, i.e. the claims are not limited to administering Ncb5or to subject having the Ncb5or deleted. Furthermore, applicants have not provided adequate guidance that Ncb5or deletion is linked to human diabetes. Therefore, applicants' arguments are not persuasive.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The rejection of claims 11, 18, 23 has been withdrawn in view of the amendment.

Claims 32-34, 45, 50, 52 and 53 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "said flavo-heme..." in claims 32 and 33 is indefinite because it lacks antecedent basis in parent claim 31 as amended.

Claim 33 is indefinite because the phrase "the amount of a reactive oxygen species" lacks antecedent basis.

Claim 34 is indefinite because "herein" should be "wherein."

Claim 34 is indefinite because "said reactive oxygen species" is dependent upon "the amount of a reactive oxygen species" in claim 33.

Claim 45 is indefinite because "a polypeptide consisting of the amino acid sequence of SEQ ID NO: 3, 4 and 5" uses mixed tenses. The phrase "selected from the group" inserted after the word "polypeptide" would overcome this rejection.

Claim Rejections - 35 USC § 102

The rejection of claims 45 and 51 under 35 U.S.C. 102(b) as being anticipated by Rosen (WO 01/55301 A2, pub date 8/2/2001) has been withdrawn because it cannot be determined that Rosen taught contacting pancreatic islet cells with the Ncb5or of SEQ ID NO: 2-5 in vivo.

Claims 9, 11, 12, 16, 18-21 and 22-25 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Rosen (WO 01/55301 A2).

Claims 16 and 21 require administering an Ncb5or polypeptide to subject for the intended use of increasing serum insulin or decreasing serum glucose levels. Dependent claims 20 and 25 require the subject suffer from or be at risk of diabetes. The claims encompass any teachings that describe administering Ncb5or to a patient with diabetes because any method that discloses administering Ncb5or to a patient with diabetes inherently discloses the intended use of increasing serum insulin or decreasing serum glucose in the preamble of claims 16 and 21.

Rosen disclosed SEQ ID NO: 1188, which is an amino acid sequence sharing 100% homology with SEQ ID NOS: 3 and SEQ ID NO: 1726, which is an amino acid sequence sharing 100% homology with SEQ ID NO: 4 (see SCORE search result for Database "A_Genseq_8" for SEQ ID NO: 3 and 4). Rosen disclosed that fragments, analogs, and derivatives thereof from SEQ ID NO: 1726 (p. 859, [276]) for therapeutic use. The uses described by Rosen include treating diabetes (see abstract provided herewith). The method described by Rosen inherently increases serum insulin and decreases serum glucose as claimed because Rosen describes the exact same step as

applicants and as claimed – Rosen taught administering Ncb5or to a patient with diabetes.

Applicants argue claim 45 has been limited to sequences not encompassed by SEQ ID NO: 1726. Applicants' argument is not persuasive.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner